UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,763	09/29/2006	Kazuwa Nakao	1254-0327PUS1	6725

2292 7590 07/24/2009

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
HOWARD, ZACHARY C

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
07/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,763	NAKAO ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17 and 22* is/are rejected.

7)☒ Claim(s) *11,14-17 and 22* is/are objected to.

8)☒ Claim(s) *1-22* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/06;11/9/06;4/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-22 are pending in the instant application.

Election/Restrictions

Applicants' election with traverse of Group II, claims 11-17 and 22, in the reply filed on 6/8/09 is acknowledged.

The traversal is on several grounds. First, Applicants argue that the International Preliminary Report on Patentability (IPER) "did not find a lack of unity of invention between the present claims" (pg 2). Second, Applicants argue that US 6,034,231 "does not break unity of invention". Third, Applicants argue that even if said patent does anticipate claims in Groups I and II, that the MPEP does not prohibit addition of the special technical feature (i.e., features not described in the prior art) during prosecution by amendment.

Each ground has been fully considered but is not found to be persuasive. The first ground is not found persuasive because consideration of lack of unity of invention in a national stage application under 35 USC 371 is not bound by the decisions of either the International Searching Authority (Chapter I) or the International Preliminary Examining Authority (Chapter II). The second ground is not found persuasive because the restriction requirement mailed 4/8/09 set forth (pg 3) the specific reasons why US 6,034,231 teaches a technical feature linking Groups I and II and Applicants' response does not provide any specific arguments as to *why* US 6,034,231 does not break unity of invention. With respect to the third ground, it is acknowledged that a special technical feature can be added to the claims during prosecution by amendment; however, in the instant case Applicants have not amended the claims in such a manner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-10 and 18-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/8/09.

Applicants' election with traverse of the species of (1) CNP-22 and (2) cartilage bones in the reply filed on 6/8/08 is acknowledged.

The Examiner here clarifies the record with regard to the species elections. At page 3 of the restriction requirement, it was stated that two elections of species were required in Group I or II. However, following this statement, three elections were set forth to species of CNP, patient, and bones. The restriction requirement should have instead indicated that these three elections were only required for Group I, and that only two species elections were required for Group II (species elections (1) and (3)). Group II does not recite the species of patient recited in Group I that concern species election (2). Applicants appear to have correctly anticipated this and have made elections only for species elections (1) and (3). For the record, species election (2) is hereby *withdrawn* with respect to elected Group II. Furthermore, on further consideration, species election (3) is *withdrawn*. The Examiner notes that the instant specification teaches that femora, tibiae, radiuses and ulnae are types of "cartilage bone", and that the art appreciates that the growth of these bones involves cartilage.

The traversal is on the ground that it "would not be an undue burden on the Examiner to perform a search of all species encompassed by the present claims".

This has been fully considered but is not found to be persuasive. Undue search burden is not a consideration regarding the unity of invention of species in a national stage application under 35 USC 371. Instead, as set forth in the restriction requirement, the species were deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL (with respect to species election (1) only).

Claims 11-17 and 22 are under consideration, in so far as they are drawn to the elected species.

Specification

The disclosure is objected to because of the following informalities:

(1) The title of the invention ("COMPOSITION FOR INCREASING BODY HEIGHT") is not descriptive because the elected invention is directed to a method for increasing body height comprising activating guanyl cyclase B. A new title is required that is clearly indicative of the invention to which the claims are directed.

(2) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the first sentence of the specification should be amended to indicate that the instant application is a 371 of PCT/JP05/06837, filed 3/31/2005.

Appropriate correction is required.

Claim Objections

Claims 11, 14-17 and 22 are objected to because of the following informalities:

(1) Claims 11, 14 and 22 use the abbreviation "GC-B" without the corresponding full name of the compound (guanyl cyclase B). The abbreviation should be spelled out completely (e.g., "guanyl cyclase B (GC-B)") in at least each independent claim.

(2) Claims 11 and 22 use the abbreviation "FGFR3" without the corresponding full name of the compound (fibroblast growth factor receptor 3).

(3) Claim 11 uses an indefinite article ("a") with a definite characteristic (i.e., "a body height of an individual" should be "the body height of an individual").

(4) Claims 14-17 use the abbreviation "CNP" without the corresponding full name of the compound (C-type natriuretic peptide).

(5) Claim 15 recites "human" (singular) as a subset of "mammals" (plural) (i.e., "mammals, including human" should be "mammals, including humans").

(6) Claim 17, line 3, has an extraneous space between "2" and the comma.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are directed to methods but do not actually recite any positive method steps (e.g., a step of administration). Instead they merely recite an intended goal (e.g., "for increasing body height" or "for extending a cartilage bone") and a mechanism (e.g., activation of GC-B), without reciting any steps to be performed that achieve the recited goal.

Claim 13 is also indefinite because the elements recited in the claim do not constitute a proper Markush group. The claim is indefinite in the alternative use of “and/or” because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

Claim 15 is also indefinite because it is unclear whether "from mammals, including human" indicates that the CNP is from a single mammal (selected from a group of mammals including humans) or is from multiple mammals simultaneously (i.e., a mixture of CNP from mammals, including human).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 15 recites the broad recitation "mammals", and the claim also recites "including human, or birds" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-17 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 11-17 and 22 are directed to methods that recite no particular method steps that require the hand of man. Thus, the claims encompass subject matter that includes naturally occurring *in vivo* activation of guanylyl cyclase B (GC-B) by its natural ligand C-type natriuretic peptide (CNP). In the absence of the hand of man, a naturally occurring process is considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for increasing the body height of a growing individual, comprising activating GC-B by administering to an individual experiencing endochondral ossification as part of growth and free from FGFR3 abnormality a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or

addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 and wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP,

does not reasonably provide enablement for method for increasing a body height of an individual, comprising activating GC-B to increase the body height in an individual free from FGFR3 abnormality. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention of claims 11-17 and 22 is a method of increasing body height by activating guanyl cyclase B (GC-B; also known as guanylyl or guanylate cyclase B in the prior art). GC-B is "the type B natriuretic peptide receptor (NPR-B)"; "transduces an extracellular signal to intracellular production of cGMP" and "is the receptor for C-type natriuretic peptide [CNP]" (see pg 1024 of Schulz, 2005. Peptides. 26: 1024-1034). Thus, CNP is a specific natural ligand for the GC-B receptor.

The specification teaches two naturally-occurring human forms of this peptide: CNP-22 (SEQ ID NO: 1) and CNP-53 (SEQ ID NO: 2). CNP-53 fully comprises CNP-22 as CNP-22 is identical to residues 32-53 of CNP-53. The art teaches that "[m]olecular cloning of the CNP precursor in the pig, rat, human and mouse has revealed that the primary structure of CNP-22 is identical in these species … two amino-acid substitutions are noted in CNP-53 between human and porcine/rat/mouse precursors"; pg 331 of Komatsu et al, 2002. J Bone Miner Metab. 20: 331-336). The two differences are at positions 17 and 28 in the CNP-53 sequence. Chicken CNP-22 has a single difference (position 9) from pig, rat and human CNP-22.

The specification includes Examples 1-6 in support of the claimed invention, which describe construction and characterization of a transgenic mouse that overexpresses murine CNP-22 (identical to human CNP-22). As disclosed in Example 1, this transgene is under the control of SAP promoter [serum amyloid protein]. Example 4 reports high levels of expression of the transgene product in the liver (24-fold increase) and blood plasma (10-fold increase). The specification further teaches that the "naso-anal lengths of the female and male CNP transgenic mice were both greater than those of the normal littermates, demonstrating that the increase in body height has been accelerated" (pg 22). Example 6 describes the histology of the growth cartilage of the femur of the CNP transgenic mice, reporting that "the thickness of the growth cartilage layers were greater with statistical significance than those of normal mice" (pg 23). The working examples are supported by the post-filing date publication of Yasoda et al (2008. Endocrinology. 150: 3138-3144). Yasoda et al teach that CNP and its receptor GC-B comprise a "potent stimulatory system for endochondral bone growth" and are both "expressed in proliferative and per-hypertrophic chondrocyte layers of the growth plate" (pg 3138). Yasoda et al further teach that "loss-of-function mutations affecting GC-B … cause one form of autosomal recessive human skeletal dysplasia ... indicating that the CNP/GC-B system is crucial for endochondral bone growth in humans as well as mice" (pg 3138).

The teachings of the specification and relevant art support enablement for the claimed method in so far as they are directed to a method for increasing the body height of a growing individual, comprising activating GC-B by administering to a growing individual experiencing endochondral ossification and free from FGFR3 abnormality a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 and wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP. The specification lacks enablement for the full scope of the claims for the following reasons.

(1) The specification does not enable the claimed method wherein the individual is not experiencing endochondral ossification as part of growth. The working examples

in the specification are directed solely to transgenic mice that experienced increased levels of serum CNP continuously throughout growth. No examples are provided wherein administration of CNP increases the body height of an adult (post-puberty) individual. Furthermore, in view of the teachings of the relevant art, the skilled artisan would not predict that administration of CNP to a post-pubescent individual would result in any increase in body height. Newman et al (2003. Clin Genet. 63: 241-251) teach that "[t]he vertebrate skeleton is formed by two processes, intramembranous and endochondral ossification. Intramembranous ossification forms the calvarium, mandible, and increases long bone diameter by the peripheral addition of new bone at the osteogenic front. Endochondral ossification is a developmental process, which forms the remainder of the skeleton, by replacing a cartilaginous model of the skeleton with bone. This is a highly complex, temporally and spatially co-ordinated process" (pg 242). The chondrocytes involved in endochondral ossification form a "growth plate" comprising four zones (Figure 1 of Newman et al), In the last zone (hypertrophic zone), the "cartilaginous matrix is mineralized" and "replaced by trabecular bone" (pg 242). Newman et al further teach that the process of endochondral ossification begins during the fifth week of human development and continues "until puberty when the growth plate is replaced by bone" (pg 243). It would require undue experimentation for the skilled artisan to determine how CNP could increase body height in a post-pubescent individual wherein the process (endochondral ossification) acted upon by CNP has ceased.

(2) The scope of claims 11-13 and 22 is such that any means of activation of GC-B is encompassed by the claims. While the specification teaches that a GC-B activator can be a "peptide or a nonpeptidic low-molecular-weight compound, preferably a CNP peptide or a derivative thereof, that can bind to and activate GC-B, which is known as a CNP receptor" (pg 16), claims 11-13 and 22 encompass any peptide, protein, nucleic acid, lipid, carbohydrate, antibody, or other organic or non-organic compound that can activate GC-B. However, the only GC-B activators actually disclosed in the specification are CNP peptides. The specification provides no guidance on selection of other compounds for activation of G-CB.

The instant fact pattern is similar to that in *In re Hyatt*, 708 F.2d 712, 218 USPQ

195 (Fed. Cir. 1983), wherein a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). As discussed above, the claims encompass any peptide, protein, nucleic acid, lipid, carbohydrate, antibody, or other organic or non-organic compound as an activator of GC-B. However, claims 11-13 and 22 fail to recite any structural limitations, and thus the skilled artisan would have to resort to trial and error experimentation to identify compounds meeting the functional limitations of the claim. Such experimentation is considered undue. While the skilled artisan could engage in experimentation to screen compounds in a screening assay, this too would require undue experimentation in view of (1) the essentially limitless, structurally diverse compounds that could be screened; (2) the fact that even if many compounds were screened, there is no assurance that any compounds will be found and (3) the further requirement to test each compound to determine whether there is a correlation between the *in vitro* and *in vivo* activity (as was done with CNP-22 in the instant examples).

Due to the large quantity of experimentation necessary to determine what structural features are required for activating GC-B as well increasing body height; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the unpredictability of activating GC-B as well increasing body height; and the breadth of the claims 11-13 and 22 which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 14-17 are limited to activation of GC-B by a C-type natriuretic peptide (CNP) or a derivative thereof. The specification and claim 17 indicates that a "derivative" thereof encompasses mutations that include deletions, substitution or addition of one or

more amino acids to human CNP-22 (SEQ ID NO: 1) or CNP-53 (SEQ ID NO: 2) and that possess a "CNP activity". No limit is placed on the number of changes as long as a "CNP activity" is present. The specification teaches that "CNP activity" includes "the activity to act on GC-B to increase guanyl cyclase activity or the activity to increase the body height of an individual" (¶ 68 of the published application). Claims 15 and 16 are also considered to encompass "a derivative" of a CNP of the same scope because they depend from claim 14, and thus the recitation limits both the CNP and the "derivative"; i.e., claims 14 and 15 are broadly interpreted to encompass a CNP of SEQ ID NO: 1 or 2 or a derivative thereof.

The specification further teaches that derivatives of CNP-22 are described in "Japanese Patent Publication (Kokai) No. 6-9688 (1994)" and "International Publication No. WO/02/074234". These publications do not appear listed on either the IDS of 9/29/06, 11/9/06 or 4/9/09. The Examiner has not been able locate a JPO document with the number 6-9688. Applicants are requested to submit this document if it provides support that goes beyond that disclosed in the WO/02/074234. The Examiner has located WO/02/074234 (Golembo et al) and listed it on the PTO-892 accompanying this office action. In Example 6 (pg 21-24), the '234 publication describes "CNP analogs", including truncated versions (17-mers, 15-mers, 14-mers, 13-mers, 12-mers and 11-mers) with or without 1-3 substitutions, as well as the "% relative binding" of each (Tables 2 and 3). Example 6 states that "All peptide variants were analyzed for activity using the Biotrak enzyme immunoassay … that measures the amount of secondary messenger, cyclic GMP, elicited after activation of the natriuretic peptide receptor by the peptide on C3H10T1/2 cells" (pg 22). It appears that the "% relative binding" listed in the Tables reflects the result of this assay. As shown in Table 2, even truncated variants as small as 11 amino acids in length (11-mers) retained a small degree of activity (~3-4%). However, Table 3 also shows that particular single amino acid substitutions in a 17-mer result in a relative binding that is less than zero (negative), presumably because they had less activity than the control.

In view of the teachings of the prior art (i.e., the '234 publication), the skilled artisan could practice the claimed methods with a CNP of SEQ ID NO: 1 or 2, a

mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP. However, the skilled artisan would not know what additional mutations to make in the CNP and still retain activity. The skilled artisan could make and test further mutations in a screening assay, but this would require undue experimentation in view of (1) the essentially limitless number of mutations encompassed by the claims and (2) the evidence provided by Table 3 of '234 publication that many mutations, even single substitutions, in the CNP sequence result in a loss of activity.

Due to the large quantity of experimentation necessary to use the full scope of the variants of CNP encompassed by the claimed methods, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the invention of claims 14-17 with respect to the full scope of CNP variants encompassed by the claims.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 11-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claims 11-13 and 22 are genus claims because the claims are directed to methods of using a genus of means of activating G-CB. The genus is highly variant because a significant number of structural differences between genus members are permitted. The claims potentially encompass use of peptides, protein, nucleic acid, lipid,

carbohydrate, antibody, other organic or non-organic compound, or even radiation, with the ability to activate GC-B. Claims 14-17 are genus claims because the claims are directed to methods of using a genus of derivatives of CNP. The claims potentially encompass derivatives with an unlimited number of mutations with respect to CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2, and with "CNP activity".

However, the specification fails to disclose any compounds with the ability to bind G-CB and increase intracellular production of cGMP and that have a structure different than a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the full scope of the genus of GC-B activators or CNP derivatives. Structural features that could distinguish the GC-activators or CNP derivatives with activity beyond those CNP derivatives with 1 to 10 amino acid mutations are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written

description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of GC-B activators, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

While the specification discloses screening assays for identifying compounds that have the ability to ability to bind to G-CB and increase intracellular production of cGMP, such assays are not sufficient to indicate that Applicants had possession of the genus of compounds at the time of filing. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method for increasing the body height of an individual, comprising activating GC-B by administering to an individual free from FGFR3 abnormality a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 and wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyazawa et al (2002. Endocrinology. 143(9): 3604-3610).

The recitation of "for increasing a body height of an individual" in the preamble of claim 11 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Furthermore, the recitation of "to increase the body height in an individual free from FGFR3 abnormality" in the method steps of claim 11 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art, except in so far as it limits the method to a particular patient population (an individual free from FGR3 abnormality). Furthermore, C-type natriuretic peptide (CNP) is inherently a compound that activates GC-B (as evidenced by dependent claim 14). Furthermore, the instant specification defines a "FGFR3 abnormality" as referring to achondrogenesis or achondroplasia caused by growth inhibition of cartilage bones resulting from mutations in the FGRF3 gene; thus an "individual free from FGRF3 abnormality" includes any individual without a mutation in FGRF3. Therefore, claim 11 encompasses a method comprising activating GC-B using CNP in an individual without a FGRF3 mutation.

Miyazawa et al teach a transgenic mouse that overexpresses CNP in a wildtype background (pg 3605). The mouse was generated by "targeted expression of CNP in the growth plate chondrocytes under control of the mouse pro-α1 (II) collagen (Col2a1) promoter. These mice do not have a mutation in the FGFR3 gene. Therefore, Miyazawa et al teach a method comprising activating GC-B using CNP in an individual without a FGRF3 mutation, which anticipates claim 11.

It is noted that even though the intended use of claim 11 is non-limiting with respect to the prior art, the teachings of Miyazawa et al also meet the recited intended use. The term "body height" is not defined in the instant specification and has been broadly interpreted as encompassing body length for a mouse, particularly in view of Example 5 which equates the length of mice with body height. Miyazawa et al further teach that "CNP-TG mice exhibit kyphosis and elongated limbs, paws and tails, which are similar to that found in BNP-Tg mice" and "[a]t birth, there are no significant differences in the naso-anal length among genotypes" but at "5 wk of age, CNP-TG mice grow larger ... than wild-type mice. The naso-anal differences among these animals increase progressively until 10 wk of age … [and] are unchanged thereafter" (pg 3605). Miyazawa et al further teach that "[s]oft x-ray analysis revealed that CNP-Tg mice have longer vertebral bodies, tails, and extremities compared with wild-type mice at 25 wk of age" (pg 3605). Thus, Miyazawa et al teaches that the method encompassed by claim 11 that also meets the intended use of said claim (an increase in body height in an individual).

Claims 12 and 13 each encompass a method of claim 11 wherein the increase in body height is due to an extension of cartilage bones that are tibiae. Thus, each dependent solely limits the intended use of claim 11, and is therefore anticipated by Miyazawa et al for the same reason as claim 11. However, the teachings of Miyazawa et al also meet the recited intended use of claim 12. Miyazawa et al further teach that "[t]he height of the proliferative and hypertrophic chondrocyte zones in tibias from CNP-Tg mice increases prominently" (pg 3606). Thus, the increase in length of the transgenic mice is due to an extension of tibiae (a form of "cartilage bone").

Claim 14 depends from claim 11 and encompasses GC-B activation by CNP. Claim 14 is anticipated by Miyazawa et al for the same reasons as claim 11.

Claim 15 depends from claim 14 and limits the CNP to CNP-22 or CNP-53 from mammals or birds. CNP-53 is a precursor of the CNP-22 peptide. Thus, the transgenic mice taught by Miyazawa et al would produce both CNP-53 and CNP-22. Therefore, claim 15 is anticipated by Miyazawa et al for the same reasons as claim 11.

Claim 16 depends from claim 14 and recites that the CNP is the CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2. SEQ ID NO: 1 and 2 are disclosed as human sequences in the instant Sequence Listing. However, mouse CNP-22 sequence is inherently identical to the human CNP-22 sequence of SEQ ID NO: 1 ("[m]olecular cloning of the CNP precursor in the pig, rat, human and mouse has revealed that the primary structure of CNP-22 is identical in these species"; pg 331 of Komatsu et al, 2002. J Bone Miner Metab. 20: 331-336; cited herein solely to provide evidence of inherency). Parent claim 14 also includes derivatives of the recited CNP; therefore, dependent claim 16 also includes derivatives of the recited CNP sequence. Thus, claim 16 encompasses also encompasses derivatives of SEQ ID NO: 1 or 2. Such derivatives encompass the mouse CNP sequences as used by Miyazawa et al. Therefore, claim 16 is anticipated by Miyazawa et al for the same reasons as claim 11.

Claim 17 depends from claim 14 and encompasses a derivative that has a deletion of one or several amino acids with respect to SEQ ID NO: 1 or 2, while possessing a CNP activity. As explained above for claim 16, the recited "derivatives" of SEQ ID NO: 1 or 2 (human sequences) encompass mouse sequences. Furthermore, CNP-22 contains 31 amino acids that are deleted with respect to CNP-53; conversely, CNP-53 contains 31 amino acids that are added with respect to CNP-22. Therefore, claim 17 is anticipated by Miyazawa et al for the same reasons as claim 11.

Claim 22 is an independent claim; The recitation of "for extending a cartilage bone free from FGFR3 abnormality in an individual" in the preamble of claim 22 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Therefore, claim 22 encompasses activating GC-B in an individual with bones free from FGFR3 abnormality. Claim 22 is anticipated by Miyazawa et al for the same reasons as claim 11.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647